Testing altered learning in the D2 corticostriatal pathway with antipsychotic exposure

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Background

Antipsychotic medications can be successful in alleviating the positive symptoms of psychosis, such as delusions and hallucinations, but are **unsuccessful at treating the negative symptoms of schizophrenia**, including emotional flatness and lack of motivation. Antipsychotic medications, such as Haloperidol, are Dopamine D2 receptor blockers and are involved in learning, motivation, reward, movement and coordination.

Why Study This?

There is evidence that a **blockade of D2 receptors** can bias individuals to **learn more from "negative" outcomes**, and that this can be due to an altered balance of receptor activation in regions of the cortico-striatal pathway responsible for reward processing.[1] In other words, **certain pathways in the brain become strengthened such that there is a bias toward learning from negative outcomes and omission of expected rewards.**

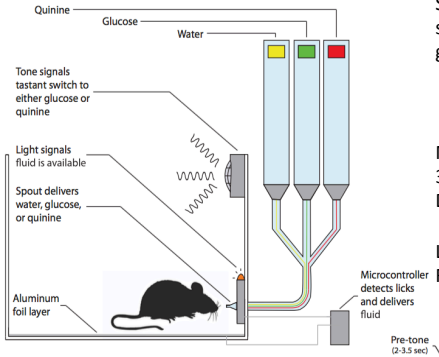
Hypothesis

Our prediction is that a long-term D2 blockade, such as during antipsychotic treatment with Haloperidol, may generate increased learning from negative outcomes and suppressed motivation, possibly contributing to lack of efficacy in the treatment of negative symptoms of schizophrenia.

Predictions:

1) Faster learning of lick suppression to quinine cue in antipsychotic exposed animals
2) Less licking to glucose cue in antipsychotic exposed animals
3) Persistence of avoidance after stopping drug exposure

Approach/Avoidance Task and Methods

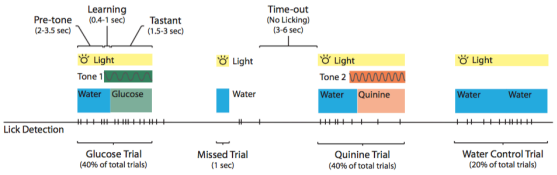


Series of trials, where tone (4KHz or 11KHz) cues that a single spout will change from delivering water to either glucose (10%) or quinine (10mM)

Water: 200-3500 ms
Tone: 400-1000 ms
Tastant: 1500-3000 ms

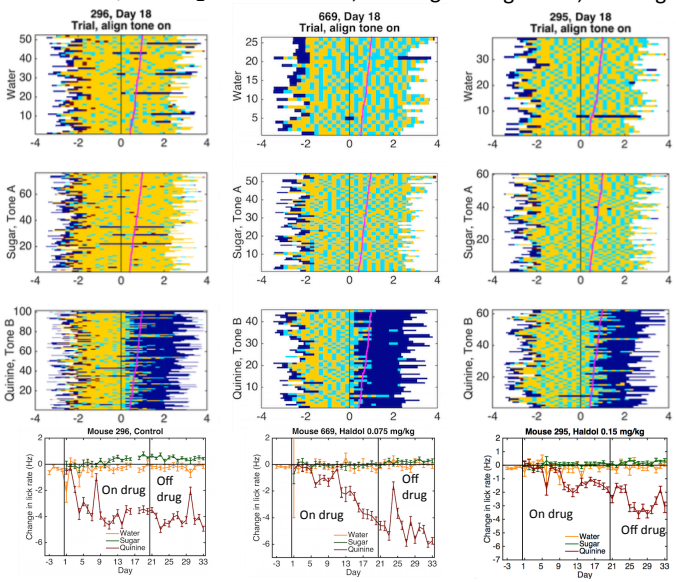
Mouse must lick to light cue within 1s and suppress licking 3-6s between trials; Fluid delivery 5-20 licks, fixed per trial
Day 1 is start of drug/tones/tastants

On drug days 1-20, off drug days 21-33 (13 days)
Low drug dose = 0.075 mg/kg, high dose = 0.15 mg/kg
Four mice age 5 mo. at task start, four mice age 8 mo.
Male CL7/BL6, n=4 control, n=2 high Hal, n=2 low Hal



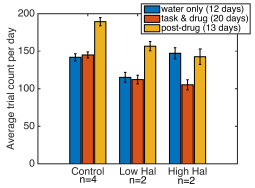
Lick Rate Plots (top) and Learning Curves (bottom), 3 Example Mice

Control, learning | Low dose, learning | High dose, learning

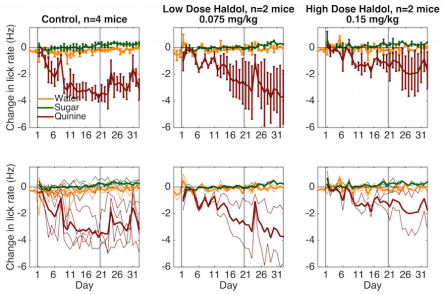


Conclusions:

- Control mice showed early positive learning (day 5). Haloperidol mice did not show early positive learning.
- Avoidance data are inconclusive due to low animal number, but data indicate mice on haloperidol are capable of learning task.
- One low dose mouse (ear tag 669, 0.075 mg/kg haloperidol) learned very well, and was the strongest performing mouse post-drug. We will use this dose for future testing.
- Mice on high dose haloperidol performed fewer trials than prior to drug exposure and recovered post-drug. Trial counts did not shift for low dose haloperidol mice on drug.



Pooled plots of learning, by injection type



Acknowledgements

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[1]Maia, T.V., Frank, M.J., *From reinforcement learning models to psychiatric and neurological disorders.* Nature Neuroscience, 2011. **14**(2): p. 154-62.